periments allowed correlations between site-specific proton assignments[3] and ^{13}C chemical shifts to be made. These site-specific ^{13}C shifts were then compared to the 1D chemical shifts, and the 1D chemical shifts were assigned accordingly. These assignments are marked with superscript italic c in Table I. All of the others are degenerate or within 0.1 ppm of the other, and are correctly assigned according to carbon class.[19]

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Supplementary Material Available: Figures S1 and S2 containing details of the same spectrum as Figure 1 etc., level 2.5 lower than Figure 1, and cross peaks A8(H8-C5), G3(H8-C5), and G5(H8-C5) and G5(H8-C4) and G3(H8-C4), respectively (2 pages). Ordering information is given on any current masthead page.

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Control of Reaction Rates in Vesicular Systems

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Vesicles prepared with synthetic amphiphiles catalyze numerous reactions with high efficiency.[1-5] Several studies have attempted to separate the kinetic and mechanistic effects of outer and inner surfaces of such vesicles on various chemical reactions.[5] We here report that a negatively charged substrate (5,5′ dithiobis(2-nitrobenzoic acid)) (DTNB) can be selectively incorporated in the inner and/or outer surfaces of vesicles prepared with a positively charged amphiphile (dioctadecyldimethylammonium chloride) (DODAC). Selective incorporation permitted the demonstration of similar interfacial catalysis of the alkaline hydrolysis of DTNB[3] by both surfaces. We also demonstrate here, for the first time, that the ratio of the rates of reaction at the inner and outer surfaces can be modulated by changing the composition of the medium.

DTNB (Sigma Chem. Co.) was incorporated in large unilamellar DODAC (Herga Ind. Quim. Brasil) vesicles by injecting a $CHCl_3$ solution of DODAC (20 mM) into an aqueous solution (70 °C)[6] containing 5 mM NaCl, 90 mM erythritol, and 0.15 mM DTNB, pH 5.3. This preparation was annealed,[7] and aliquots were filtered through two columns of Dowex 21K (Cl) (Serva Fine Chemicals)[8] and eluted with 5.0 mM NaCl/90 mM erythritol. This procedure led to vesicles in which DTNB was adsorbed only to the internal surface.[9] DTNB hydrolysis (30 °C) was followed (437 nm)[3] in a Beckmann DU7 spectrophotometer.

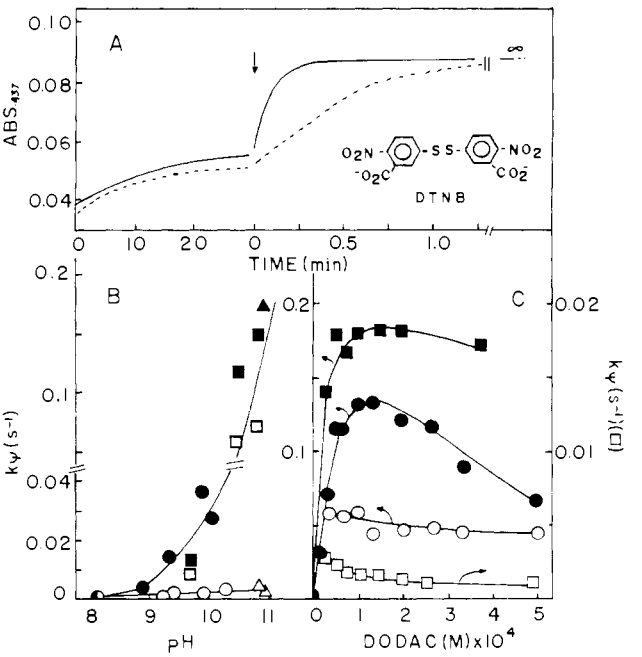

Figure 1. A. Chloride and bromide effects on the endo- and exovesicular hydrolysis of DTNB. [DODAC] = 5.3×10^{-5} M, [DTNB] (endovesicular, analytical) = 2×10^{-6} M. The arrow indicates the addition of external DTNB 2×10^{-6} M final concentration): (—) NaOH 1 mM, NaCl 4 mM, pH 10.9; (--) NaOH 1 mM, NaBr 4 mM, pH 10.8. B. pH effects on the rate of the endo- and exovesicular hydrolysis of DTNB: [DTNB] (endovesicular, analytical) = [DTNB] (exovesicular) = 2×10^{-6} M; [DODAC] = $4*10^{-5}$ M. NaCl was added to maintain the total anionic concentration at 5 mM. Full points indicate exovesicular, and open points refer to the endovesicular reactions, respectively: (●, ○), borate buffer, 5 mM; (■, □), triethylammine·HCl buffer, 5 mM at pH 9.7, 3.3 mM at pH 10.5, and 10 mM at pH 10.9; (▲, △), NaOH 1 mM. C. Effect of DODAC concentration on the rate of endo- and exovesicular hydrolysis of DTNB. [DTNB] (endovesicular, analytical) = [DTNB] (exovesicular) = $2*10^{-6}$ M. NaCl was added to maintain the total ionic concentration at 5 mM. Full points indicate exovesicular, and open points refer to endovesicular reactions, respectively: (●, ○) triethylammine·HCl buffer, 3.3 mM, pH 10.5; (■, □) NaOH 1 mM, pH 10.91.

The endovesicular reaction was started by adding aliquots of the (column-eluted) vesicle pool (0.6 mM DODAC[10] and 0.03 mM DTNB) to a solution at the desired pH with osmolarity and ionic strength controlled with erythritol and NaCl, respectively. After the complete reaction 2 μL of a 1 mM aqueous solution of DTNB was added to the same cuvette. The ensuing absorbance increase was attributed to reaction at the external vesicular surface since (a) the rate constant[11] for this exovesicular process was similar to one obtained previously[3] and (b) DTNB does not penetrate the bilayer under our conditions.[9] Figure 1A shows a typical endo- and exovesicular hydrolysis of DTNB. Using the same procedure, kinetic data were obtained under several conditions (Figure 1B, Table I). In the absence of buffer and at high pH, the exovesicular reaction was 100 times faster than the endo process (Figure 1 (parts B and C), Table I). However, with borate or triethylammine buffers, the endo- and exovesicular rate constants were of the same order of magnitude (Table I, Figure 1 (parts B and C)). The maximum rate enhancement in the presence of vesicles, with respect to the uncatalyzed reaction, was 200-fold (Table I). The (low) rate observed for endovesicular

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(11) The rate constants were obtained from a computer-fit of a first-order process. After passage through ion-exchange columns the kinetics revealed approximately 10% of exovesicular reaction in the absence of added buffer.

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Table I. Effect of Buffer Composition on the Endo- and Exovesicular Rates of Hydrolysis of DTNB[c]

buffer composition[a]	pH	DODAC (M) × 10^5	k_1[b] (s^{-1}) × 10^3	k_2[b] (s^{-1}) × 10^3	k_2/k_1
borate 5 mM, NaCl 2.5 mM	9.2	5.3	2.0	5.6	2.8
borate 5 mM, NaBr 2.5 mM	9.2	5.3	1.8	3.7	2.1
NaOH 1 mM, NaCl 4 mM	10.9	5.3	2.0	180	90
NaOH 1 mM, NaBr 4 mM	10.8	5.3	3.3	44	13.3
triethylammine·HCl 5 mM	9.7	5.3	7.8	13	1.7
triethylammine·HBr 5 mM	9.7	5.3	6.2	3.9	0.6
triethylammine·HCl 10 mM	10.8	13	72	160	2.2
triethylammine·HBr 10 mM	10.9	13	98	63	0.6

[a] All buffer, vesicle, and salt solutions contained erythritol (90 mM). [b] Observed pseudo-first-order rate constants for the endovesicular (k_1) and exovesicular (k_2) reactions, respectively. [c] DTNB concentration was 2.0×10^{-6} M for both endo- and exovesicular reactions. The second-order rate constant for the alkaline hydrolysis of DTNB, calculated from ref 3, was 0.818 M^{-1} s^{-1} (30 °C).

hydrolysis at high pH in the absence of buffer may be attributed to rate-limiting $^-$OH permeation. Endovesicular rates limited by $^-$OH diffusion have been reported.[5c] Buffers containing neutral species can accelerate the rate of $^+$H/$^-$OH permeation across bilayers.[5b,12] The similarity of endo and exovesicular rates in this system can be understood in terms of similar reactivities at the inner and outer surfaces and of faster permeation rates for $^-$OH with buffers.

Addition of bromide produced a decrease in the rate of the exovesicular reaction, not affecting the endovesicular process (Figure 1A, Table I). The ratio between the exo- and endovesicular rate constants (k_2/k_1) can even be reversed by the addition of external salts (Table I). The inhibitory effect at the outer surface was attributed to a $^-$OH/$^-$Br exchange.[13] The permeability of halide ions is (at least) 1000 times less than $^+$H/$^-$OH for the same bilayer.[14] Therefore a bromide inhibitory effect on the endovesicular reaction was not to be expected since the (externally) added ion did not penetrate during reaction.

The DODAC concentration-dependence of the exovesicular reaction was identical with that previously reported[3] (Figure 1C). The endovesicular rate constant decreased slightly with [DODAC] irrespective of the buffer (Figure 1C). These results were rationalized by using the pseudophase ion-exchange formalism.[13] Thus, an increase in [DODAC] leads exclusively to a displacement of the externally bound $^-$OH since the concentration of free $^-$Cl increases with [DODAC] only in the external aqueous compartment. Since the concentration of free $^-$Cl in the internal aqueous compartment does not change with [DODAC] the local concentration of (internally) bound $^-$OH was not a sharp function of [DODAC]. The small decrease of the exovesicular rate constant with [DODAC] can be attributed to the lower local concentration of externally bound $^-$OH and thus a lower $^-$OH penetration rate.

In conclusion, we have demonstrated that the effects of the internal and external surfaces of DODAC vesicles on the alkaline hydrolysis of DTNB are similar. Moreover these results show that the rate of the endo- and exovesicular reactions can be controlled by the rate of reagent permeation and also by the nature (and concentration) of the ions present in both inner and outer aqueous compartments. Since vesicles prepared with synthetic amphiphiles are extremely efficient catalysts,[1-6] the control of both site and rate of reaction opens new perspectives in the understanding and use of these and other microreactors.

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Double Alkylation of α,β-Unsaturated Acetals. An Inverse Polarity Approach

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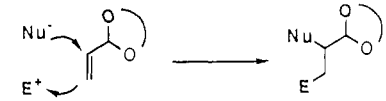
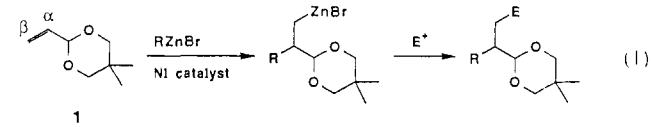
Regiochemistry of enolate formation-alkylation sequence (double alkylation) can often be controlled very effectively via Michael additions;[1] Noyori's prostaglandin synthesis immediately comes to mind.[2] Reported herein is an umpolung[3] version of the process, and the general scheme is illustrated below.



We have found that an α,β-unsaturated acetal undergoes rapid metalation upon treatment with allylzinc in the presence of nickel catalyst. Allylzinc reagent, as a nucleophile, attacks at α carbon of the acetal **1**, and then the resulting carbanion at β-position reacts with a variety of electrophiles to afford α,β-dialkylated acetal effectively, eq 1.



(1)

1

Copper-[4] or nickel-[5]catalyzed reaction of the Grignard reagent with α,β-unsaturated acetals was reported to produce only the corresponding Michael-type addition (β-alkylation) products in moderate yields. In some cases, the more reactive allylic Grignard reagent reacts with nonactivated double bonds.[6] Allylic zinc reagents, in contrast, are relatively unreactive toward alkenic bonds.[6b,7]

Treatment of 1 equiv of α,β-unsaturated acetal with a solution of allylzinc bromide (3.5 equiv) in CH_2Cl_2[8] under the influence

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